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| 1646 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/063,712 | EATON ET AL. | |
| | Examiner | Art Unit | |
| | Claire M. Kaufman | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4-14 and 16-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-14 and 16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Basis for Claim Amendment*

It is noted that the basis for the claim amendment adding the fragments of SEQ ID NO:80 is presumed to be the non-transmembrane domains. See Figure 80.

### *Inventorship*

In view of the papers filed 8/8/05, the inventorship in this nonprovisional application has been changed by the deletion of D.L. Eaton, J. C. Grimaldi, M. E. Gerritsen, C. K. Watanabe and E. Filvaroff.

### *Response to Amendment*

Applicants discuss the Declaration of Godowski, however, this declaration was not filed in the instant case. Because it was filed in a sister case with substantially the same issues, the declaration and arguments related to it will be addressed to further compact prosecution. However, Applicants should file a copy of the declaration in the instant case for completeness of record.

The Declaration of Godowski under 37 CFR 1.132, is insufficient to overcome the rejection of claims 4-114, 16-31 based upon 35 USC § and 112, first paragraph, as set forth in the last Office action for claims 4-14 and 16-20 and as applied here to new claims 21-31 because: it does not establish that the skilled artisan could use the claimed invention without undue experimentation.

The Declaration of Godowski under 37 CFR 1.132 is sufficient to overcome the rejection of claim 4-20 based upon 35 USC 101 because of the experimental description in the declaration and further consideration including consideration of the art cited in the declaration.

### *Response to Arguments*

The rejection of claims 1-3 and 15 is moot in view of the cancellation of the claims.

The rejection of claims under 35 USC 101 is withdrawn in view of the Declaration of Godowski ~~filed 8/8/05~~ and upon further reconsideration. This rejection will not be applied to

new claims 21-31. However, the rejection under 35 USC 112, first paragraph, enablement is maintained for claims 4-14 and 16-20 and applied to new claims 21-31.

The rejection of claims 4-13 under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of the amendment to the claims. However, claims 14, 16-21 and new claims 14-17 are rejected below.

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims. A new rejection appears below.

The rejection of claims under 35 U.S.C. 102 are withdrawn in view of arguments made in a related case that in view of the "Stempel Doctrin". That is, because the prior art relied upon teaches no more than Applicants' earliest priority application which discloses SEQ ID NO:79 and 80, Applicants are entitled to a priority date of 9/10/98 (60/099,792) for the purposes of those references previously relied upon. However, a new rejection appears below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

Claims 6, 9,10, 14, 26, 27 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because there cannot be "a polypeptide of SEQ ID NO:80." SEQ ID NO:80 is only one polypeptide. There could, however, be a fragment of SEQ ID NO:80.

### *Claim Rejections - 35 USC § 112, First Paragraph*

Claims 4-14, 16-20 remain and claims 21-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as set forth in the previous Office action and for the following reasons addressing the new claims:

New claims 14-17 are drawn to a polypeptide that hybridizes under stringent conditions to SEQ ID NO:79 or a nucleic acid encoding SEQ ID NO:80 or any of four particular fragments of SEQ ID NO:80 (see sections (c) and (d) of claim 14, for example), with or without the signal peptide, and which can be used as a primer or probe and which is at least 20 nucleotides in length. No function has been attributed to any of these fragments. While it has been shown that the polypeptide of SEQ ID NO:80 can induce release of TNF-α in blood, one would not expect any of these small fragments to have that function, the largest of which is 81 amino acids, only 35% of the total length of SEQ ID NO:80. There is no guidance or description in the specification to allow the skilled artisan to reasonably predict if any of the designated fragments has a specific and substantial function. Further, for the reasons previously set forth and as discussed below, the nucleic acid of SEQ ID NO:79 or which encodes the polypeptide of SEQ ID NO:80 is not enabled, so a nucleic acid that can be use as a probe of primer is likewise not enabled since the antibody *pre se* is not enabled, *i.e.*, has no therapeutic or diagnostic function. Note there is no limitation for what the primer or probe may bind. The hybridizing nucleic acid may be completely unrelated by sequence to SEQ ID NO:79 due to the hybridizing limitation.

Applicants arguments which pertain to the enablement rejection under 35 USC 112 will be addressed here.

First, to understand why it is maintained that it would require undue experimentation to use the claimed invention, evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is. As to the nature of the invention, it is a nucleic acid which may encode protein that can cause release of TNF-α in blood. No other specific and substantial functions were recognized at the time the invention was made and the encoded polypeptide was not known to be related to a highly conserved family of polypeptides with a well-recognized structure/function relationship from which the function of PRO1356 could be inferred. The primer/probe nucleic acid of claim 14 has no limitation as to what it can and cannot bind. The claimed nucleic acids not identical to SEQ ID NO:79 or which do not encode the polypeptide of SEQ ID NO:80 have not been shown to exist in nature and the specified fragments of SEQ ID NO:80 have been shown to have no activity themselves. As to the state of the prior art, other structurally related polypeptides had

been found, but no connection of SEQ ID NO: 80 to TNF was known. While the skill in the art for therapeutic use of TNF and antagonists of TNF has existed for at least a decade, the skill in the art related to endogenous TNF release in blood by factors was low. There are no working examples of the effects of *in vivo* intravenous (*i.v.*) administration of PRO 1356 and the effect on release of TNF-α in blood. More importantly there are no examples of proteins not identical to PRO1356 (including fragments and proteins 95% identical to SEQ ID NO:80) that can cause release of release of TNF-α in blood *in vitro* or *in vivo*. The breadth of the claims is broad, encompassing great structural variation and fragments with no known function. There is very little guidance or direction about how the encoded polypeptide of SEQ ID NO:80 can be altered while retaining the ability to stimulate release of TNF-α in blood. As discussed in the previous Office action, there is also a lack of guidance about which if any tumors TNF-α released into the blood can effect, what the blood concentration of TNF-α must be to have a significant useful physiological effect, how the inducing polypeptide can be administered without the undesirable non-tumor cytotoxic activity outweighing the benefits of anti-tumor effects, how the side effects of TNF-α such as inflammation can be handled, and how the leap can be made from release of TNF-α from blood to having a particular therapeutic benefit. Other than encoding the polypeptide of SEQ ID NO:80, the disclosed nucleic acid of SEQ ID NO:79 has not utility. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

Applicants argue (p. 13) from MPEP § 2107.01, that "Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." The argument has been fully considered, but is not persuasive. According to that section of the MPEP, "A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition.... Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688

(CCPA 1973)." The present invention would fall within the former category since it is unclear what condition(s) could be treated if TNF-α was released into the blood and how treatment could be accomplished without toxicity. Beyond that, it is also unclear how much of the instant invention would be needed to produce a biologically effective amount of TNF-α release.

On page 14, Applicants cite *Fujikawa v. Wattanasin* and *Cross v. Iizuka* arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* Evidence only needs to be such that the skilled artisan would be convinced of a reasonably probability of the asserted use. The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* TNF-α release data can *per se* support use of TNF-α release for therapeutic purposes. The issue in this application is the insufficiency of disclosure to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: repeatability of response, therapeutic use of TNF-α once it has been released into **blood**, the skilled artisan cannot use the claimed invention. Even if TNF-α is released in blood *in vivo*, which has not been questioned, that alone is not sufficient for enablement if the skilled artisan does not know how to use this release based on the teachings of the prior art and specification.

Applicants argue (pages 16-18) that the declaration of Godowski, a copy of which was submitted in a sister application but not here and which will be addressed here for the sake of compact prosecution, supports the significance of the data and their use. The declaration contains experimental methodology for Example 17 as well as results. Additionally, there is a discussion of the prior art literature concerning therapeutic benefits of TNF-α and TNF antagonists, as well as patents that have issued concerning TNF and its use. The argument has been fully considered, but is not persuasive. While the declaration does support the significance of the results in terms of TNF-α release in response to PRO1356 compared to the negative control, with levels being at least 50-fold greater in response to PRO1356, and does support utility of PRO1356, there remain many issues that cause the instant invention to not have enablement. Repeatability remains an issue in that there is no information in Example 17 or the declaration about how many samples were treated with PRO1356. Additionally, while prior art and patents disclose uses of TNF-α, there is a lack of information about the effects or, more importantly, the effectiveness of TNF-α release in blood. The many references cited by

Godowski in the declaration will be addressed in turn as they relate to enablement of the instant invention. Also, there is no supported use for the nucleic acid that is not dependent on encoding a protein with the TNF-inducing properties of PRO1356.

Carswell et al. (#9, PNAS, 1975) is cited to support TNF anti-tumor properties, however, Carswell examined bacterial endotoxin-induced TNF release and also the effects of *i.p.* injection of TNF into mice. While *i.p.* injection of TNF did reduce the size of some tumors, *i.p.* injection is not equivalent to *i.v.* (intravenous) injection. The tumors that responded to TNF were subcutaneous transplanted tumors (paragraph bridging pages 3667-7). Additionally, the subjects tested were several inbreed mouse strains with very obvious physiological response differences (Table 3), that make generalizations from the results difficult. Eigler et al. (#10, Immunol. Today, 1997) discuss the toxicity of TNF and use of anti-TNF agents in a therapeutic manner. It must be remembered that the instant invention is not drawn to TNF antagonists, but to a polypeptide that stimulates TNF release. The use of an antagonistic antibody requires that PRO1356 exists in blood and that it endogenously plays a role in TNF-α release. That is PRO1356 must endogenously cause an undesirable release of TNF-α in blood which can then be blocked to ameliorate the negative effects of the endogenous action of PRO1356 on TNF-α release. If it does not, then administration of an anti-PRO1356 **blocking** antibody would have no effect on TNF-α and have no therapeutic effect. The specification provides no reasonable expectation that PRO1356 is either expressed in blood or causes TNF-α to be released into blood in the body such that administration of an anti-PRO1356 antagonist antibody would have any therapeutic benefit or specific and substantial utility. Therefore, basing the use of PRO1356 on its use to generate antagonist antibodies is not enabled. Goeddel (#12, Cold Spring Harbor Symposia on Quantitative Biology, 1986) was able to induce necrosis of Meth-A sarcoma intradermally implanted into inbread mice (p. 601, 2nd and 3rd paragraphs). However, it was concluded that, "The site of tumor implantation appears to be a critical factor in the demonstaration of antitumor activites of TNF-α against transplantable sarcomas...," with intraperitoneally implanted tumors being unaffected by *i.v.* TNF-α in contrast to intradermally implanted tumors. These results are very similar to those of Carswell et al. discussed above. For the same reasons, the findings cannot be generalized to support enablement for the claimed invention. There seems to be some confusion about the Hallahan et al. (#13, Nat. Med., 1995)

references cited in the declaration(3rd sentence of ¶ 7). It is said to "demonstrate that adenoviral vectors comprising the TNF-α gene were successful in treating tumors in animals." Instead, Hallahan et al. discusses the use of TNF-α in radiation therapy, finding not that it protects against the radiation, but that when injected into a tumor, it enhances killing of that tumor. Further, Hallahan et al. (p.790, col. 1, first paragraph) state, "Unfortunately, a clinical trial combining TNF-α and radiation was limited by systemic toxicity. The present work suggests that localized production of TNF-α may enhance tumour killing while avoiding systemic toxicity." Neta et al. (#14, J. Immunol., 1988) is cited as evidence that TNF-α protects against ionizing radition in the context of radiation therapy. While Neta et al. did observe some protection for mice who received *i.p.*(intraperitoneal) TNF-α from the effects of full-body ionizing radiation, it would be difficult to extrapolate those findings to a therapeutic use when taken with the problem of systemic toxicity reported by Hallahan et al. and with the consideration of when if ever the general, not localized, protection of ionizing radiation would be needed. Paleolog, (#16, Mol. Path., 1997, and #17, Expert Opin. Invest. Drugs, 2003) both discuss the therapeutic benefits of anti-TNF-α antagonist antibody treatment for rheumatoid arthritis and the 1997 article also discusses benefits in treatment of Chrohn's disease. For the reasons discussed above for Eigler et al., the reliance onuse of an antagonistic antibody to PRO1356 for enablement for the instant invention is not supported by the instant specification. It is not known if PRO1356 exists in blood, nor has it been sufficiently characterized to enable making an antagonistic antibody that inhibits release of TNF-α in blood. The skilled artisan could not predict if administration of an anti-PRO1356 antagonist antibody would have a physiological effect. The patents cited which that deal with TNF antagonist do not deal with PRO1356 antagonist. For the same reasons discussed for Eigler et al. and Paleolog et al., these patents do not support enablement of the claimed invention. It must be stated that each patent is examined on its own merit and the Examiner cannot discuss the merits of a particular patent. Of note is US 4,980,160, which shows that administration of TNF alone was fatal to all rats tested, administration of a non-steroidal anti-inflammatory decreased mortatility to only 45% of the rats dying (Example 1). At the beginning of Example 1 (col. 8, lines 41-48, it is explained, "This example represents the in vivo action of non-steroidal anti-inflammatory agents in blocking the toxic side effects of treatment with high doses of TNF. In this example, we administered TNF at a dosage which was lethal

when given by an intravenous route, due to life-threatening side effects such as hypothermia, metabolic acidosis, hypoglycemia and peripheral cyanosis." This patent was able to reduce mortaility in their rat model so only about half of the rats died. It points out the toxic effects of TNF and difficulty of using it therapeutically. Again, in US 4,894,225, tumors were subcutaneous in inbred mice (see the discussion of Carswell et al. above). For the reasons addressing the declaration including the references relied upon therein, the declaration of Godowski is not sufficient to support enablement of the instant invention.

Applicants argue on p. 16 that there is no requirement for therapeutic safety of a compound in order to establish utility. While this is generally correct for utility, it is not correct for enablement. With an intended use as a pharmaceutical or for therapeutic purposes, the examiner cannot ignore toxic effects. For example, if a compound is intended for treatment but kills the patient, the compound is not enabled for treatment. The consideration of the complexity of the action of TNF-α cannot be ignored. As discussed in the previous Office action:

> TNF-α has complex actions and interactions as discussed by Halle et al. (Exercise Immunol. Rev., 4:77, 1998, paragraph bridging pages 79-80):
>
> > TNF-α is a cytokine that can be synthesized by several cell types and has been shown to be involved in physiological states such as inflammation, cytotoxicity, immunomodulation, cellular growth, and angiogenesis. It acts on immune cells by directly inducing the release of other cyotkines such as interleukin-1 (IL-1) or granulocyte macrophage-colony-stimulating factor (GM-CSF), but has also been found to have several other effects ... such as influence on lipid metabolism and adhesion of leukocytes to endothelial cells.... In addition TNF-α together with other cytokines such as IL-1 is also involved in thermogenesis of brown adipose tissue. The effect of TNF-α is mediated by the binding of TNF-α to two distinct receptors—the TNF-α-R55 and TNF-α-R80—the former being responsible for the cytotoxic activity of TNF-α in general as well as the TNF-α insulin resistance....
>
> Tsimberidou et al. (Expert Rev. Anticancer Ther. 2(3):277, 2002, p. 277, second paragraph) discusses that, "TNF-α is involved in the pathogenesis of hematologic malignancies, such as multiple myeloma..., myelodysplastic syndrome..., acute myelogenous leukemia..., and also conditions associated with the use of allogeneic stem cell transplantation for their treatment, such as graft *versus* host disease...." As can be seen from these two references, which a plethora of other could be cited to support, TNF-α has many undesirable

> physiological effects. On the other hand, Lackie et al. in The Dictionary of Cell and Molecular Biology (p. 476) have as part of the definition of TNF-α (also called cachectin) that it "Preferentially kills tumour cells *in vivo* and *in vitro*, causing necrosis of certain transplanted tumours in mice and inhibits experimental metastases." Even though it might have potential therapeutic anti-tumor benefit, which tumors it can effect, how it can be administered without the undesirable non-tumor cytotoxic activity outweighing the benefits of anti-tumor effects, how the side effects such as inflammation can be handled, and finally, how the leap can be made from release of TNF-α from blood to having a particular therapeutic benefit with the above considerations taken together, is far from clear with the guidance and examples in the specification or prior art.

As a result, the ability to release TNF-α into the blood of an individual does not support enablement for the claimed invention.

Claims 14, 16-21 and new claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action and for the following reasons addressing the amendment and new claims: Addition of hybridizing conditions still leaves an enormous genus of nucleic acids encompassed by the invention. Likewise, addition of the limitation that the nucleic acid is useable as probe or primer carries virtually no weight since there is no designation to what it binds. Even if it did specify that it was a probe or primer that specifically bound SEQ ID NO:79, this still leaves the broad genus and would remain rejected for the reasons of record..

The claims are drawn to nucleic acids which hybridizes to a disclosed sequence. The claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry,

*whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides comprising the sequence set forth in SEQ ID NO: 79 (or the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC 203241) with or without its signal sequence, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicants argue (pages 21-22) that if there are sufficient identifying characteristics, *e.g.*, functional characteristic coupled to a structure, there is sufficient written description. In the instant application the function is expression of the nucleic acid in normal esophagus and relatively higher expression in esophageal tumor. The argument has been fully considered, but is not persuasive. The point is that **not** all polynucleotides with required structural relatedness and the limitation of being a probe or primer is not a sufficiently identifying feature. The specification does not convey to one of skill in the art, including recombinant DNA/protein technology art, that the inventors were in possession of these non-identical occurring claimed polynucleotides. The specification does not provide information so the skilled artisan could

readily envision such nucleic acids.

Applicants argue at pages 22-23 that there is sufficient written description for those claimed nucleic acids not identical to SEQ ID NO:75 with no functional limitation specified, and that the finding in the *Enzo* case support the claimed invention having adequate written description. This argument has been fully considered but is not deemed persuasive because (a) the fact situation in the *Enzo* case is substantively different from that in the instant case. The *Enzo* claims are drawn to a "composition of matter that is specific for *Neisseria gonorrhoeae*", which is then further described by ATCC deposit number and sequences that hybridize to such. It is further noted that the hybridization recitation in *Enzo* is substantively different than that herein, as it requires a comparative hybridization that demonstrates specificity of the claimed composition for one strain of *Neisseria* over another. By contrast, the instant claims have *no* functional limitations. Similarly, Example 9 of the Written Description Guidelines Training Materials is not applicable here, as the fact situation described therein is:

> The specification discloses a single cDNA ( SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO: 1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. These sequences may or may not be the same as SEQ ID NO: 1.

The nucleic acids claimed herein are not required to encode a protein, much less one with adenylate cyclase or other well-characterized activity. The fact situation therein is substantively different from that of the instant application. For these reasons and those previously of record, the rejection is maintained.

Applicants argue (pages 23-24) that the new claims should not be subject to a written description rejection since they, like Example 14 of the written description training materials, require a 95% homology and particular activity. The argument has been fully considered, but is not persuasive. Having a particular catalytic activity, as the compound in Example 14 of the

mateials, is not the same as a general property of being a probe or primer. This does not confer a particular distinguishable property.

Applicants argue (p. 24) that patents have been issued with claims to variant proteins and nucleic acids when such variants were never made. The argument has been fully considered, but is not persuasive. Each application is examined on its own merits.

### *Claim Rejections - 35 USC § 102*

The following rejections under 35 U.S.C. § 102 is made under the assumption that the effective filing date for the instantly claimed invention is 5/3/02, which is the filing date of the instant application. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. §120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the claimed invention. Because the instant application does *not* meet the requirements of 35 U.S.C. § 112, first paragraph, for the reasons given above and it is a continuing application of PCT/US00/23328 (8/24/00) which claims benefit to 60/099,792, the prior applications also does not meet those requirements for the claimed invention and, therefore, is unavailable under 35 U.S.C. § 120.

### *Claim Rejections - 35 USC § 102*

A person shall be entitled to a patent unless -
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4-6, 9, 10, 14 and 16-19, 21-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Furuse et al. (J. Biol. Chem., 153(2):263-272, 16 April 2001).

Furuse et al. teach canine Caludin-2 (Fig. 2, see also attached GenBank AF358907 cited in legend of Figure 2). The complete sequence is at least 95% identical to SEQ ID NO:80 (see attached sequence comparison) and is 100% identical in the region of amino acids 141-162. Also taught is the nucleic acid in an expression vector and host cell (*e.g.*, p. 264, col. 2, middle).

While Furuse et al. is silent with respect to the ability to induce TNF-α in blood (climas 4-5), because the canine sequence is a species homologue of the human sequence, which is 100%

identical to SEQ ID NO:80, it would reasonably be expected to possess the same major activities, including stimulation of TNF-α in blood. Also, because of its high sequence similarity to SEQ ID NO:79, it would hybridize to SEQ ID NO:79 under the conditions listed.

Claims 4-6, 9, 10, 14 and 16-19, 21-30 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. AF177340 (03 Oct 2000).

GenBank Accession No. AF177340 teaches human Caludin-2 . It has a single mismatch in the non coding region of SEQ ID NO:79 (see attached sequence comparison).

While the GenBank reference is silent with respect to encoding a protein with the ability to induce TNF-α in blood or generate antibodies to itself, because the sequence encodes a protein that is 100% identical to SEQ ID NO:80, it inherently has these properties.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuse et al. (2001) or GenBank Accession No. AF177340 as relied upon above and further in view of.

Furuse et al. (2001) do not teach canine Claudin-2 comprising a tag polypeptide or Fc region of an immunoglobulin.

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuse et al. (2001) or GenBank Accession No. AF177340 as relied upon above and further in view of Wiley et al. US 5,763,223.

Furuse et al. (2001) and GenBank Accession No. AF177340 do not teach the Claudin-2 nucleic acid in a host as required by the claims.

Wiley et al. teach nucleic acids in expression vectors transformed or transfected into CHO cell, an *E. coli* or yeast cell (cols. 11-13)

It would have been obvious to use any well known or routinely used host cell for expression of the encoded protein, including CHO cell, an *E. coli* or yeast cell for their respective desirable functions having to do with protein production. For these reasons, the instant invention is *prima facie* obvious.

***Alternative Names***

PRO 1356 is also known as Claudin-2, CLD2, CLDN2, UNQ705, HJNCT and SP82, among other names.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

October 31, 2005

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER